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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,531	03/30/2005	Paul Dent	ON/4-32419A	8871

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ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,531	DENT ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is office action is in response to applicant's request for continued examination filed on May 5, 2009.

Receipt of Declarations under 37 CFR 1.132 is acknowledged.

Continued Examination under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Status of Claims

Claims 17-22 are currently pending and are the subject of this office action.

Claims 17-22 are presently under examination.

Priority

The present application is a 371 of PCT/IB03/01418 filed on 04/04/2003, and claims priority to provisional application No. 60/371,330 filed on 04/10/2002.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (new Rejection not Necessitated by Amendment)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention

Claims 17-22 recite a method of treating Bcr/Abl-positive leukemia resistant to STI571 (Gleevec or Imatinib), comprising administering to a patient in need thereof a combination of a) a CDK inhibitor (flavopiridol in claims 119-21) and b) STI571 in the form of a pharmaceutically acceptable salt, and optionally at least one pharmaceutically acceptable carrier, in a synergistically effective molar ratio (flavopiridol/STI571) range of 1:1 to 1:10.

2. The relative skill of those in the art

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

3. The state and predictability of the art

Regarding the treatment of cancer in general, the Examiner cites Gura et. al. (Science, 1997, 278:1041-1042) and Johnson et. al. (British Journal of Cancer, 2001, 84:1424-1431).

Gura et. al., cited for evidentiary purposes, teaches that researches face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousand of drugs have shown activity in either cell or animal models, but only 39 have actually been shown useful for chemotherapy (see page 1041, first and second paragraph). Also, with regard to unpredictability, Johnson et al., also

cited for evidentiary purposes, teach that the in vivo activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer (see Results on page 1426). *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

The above articles plainly demonstrate that the art of developing and testing anticancer drugs, particularly for use in humans, is extremely unpredictable.

Regarding more specifically to the treatment of Bcr/Abl-positive leukemia resistant to STI571 (Gleevec or Imatinib) in humans, the Examiner cites: Shah et. al. (Expert Opinion on Investigational Drugs (2005) 14:89-91). Shah teaches that BCR-ABL tyrosine kinase inhibitor Imatinib has greatly improved the outcome for patients with chronic myeloid leukemia (CML). Unfortunately, mutations causing resistance to Imatinib are leading to relapses in some patients (see abstract). *In vitro* and *in vivo* data is provided for the treatment of BCR-ABL resistant cells with the SRC-ABL inhibitor BMS-354825. The authors also discuss other SRC inhibitors and Imatinib resistance like PD-180970 and PD-166326 that have shown activity in cells but due to unfavorable pharmacokinetic profiles they have not been developed for clinical use (see page 91, section 4.1, first paragraph). Also AP-23464 is active in cells; however since neither the pharmacokinetic profile not the *in vivo* activity of AP-23464 has been reported so far, it

is not known whether this drug will be suitable for clinical use (see page 91, section 4.1, second paragraph).

This clearly indicates that *in vivo* animal data is required in order to make a reasonable prediction of whether a drug that is effective *in vitro* for the treatment of BCR-ABL Imatinib resistant cells, will be effective in humans with the same resistance.

Regarding synergy, claims drawn to (unexpectedly) synergistic combinations of known ingredients must be factually supported by data commensurate in scope with the claims. See, *In re Kollman*, 201 USPQ 193 (C.C.P.A. 1979). (The court affirming a 103 rejection of a claim containing the word "synergistic", because the claims were not commensurate in scope with the showing of unexpected results, other than at 1:1 ratio for certain specific combinations).

Finally, CDK inhibitors encompass a large and diverse set of structurally different classes of compounds: from peptides to small molecules like: purine derivatives, thiazole derivatives, etc (see specification pages 2-4). Although they have the common biological property of inhibiting Cyclin Dependent Kinase (CDK), it is expected; that due to their structural differences that these CDK inhibitors will behave differently against different biological targets other than CDK.

4. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides *in vitro* data for the treatment of K562 human leukemia cells (non-resistant to Imatinib) with different concentration ratios of Imatinib and

Flavopiridol (see pages 12-14). The specification also provides *in vitro* data for the treatment of K562R human leukemia cells multi drug-resistant) with 1.5 micromolar Imatinib and 200 nanomolar of Flavopiridol for 48 hours (see pages 14 and 15). There is no data for any other CDK inhibitor, other than Flavopiridol, there is no evidence that the mixture will be synergistic at any other concentration than the one disclosed in the specification (1:1.33 Imatinib: Flavopiridol) and there is no *in vivo* data. Thus, while the specification provides in vitro data, the specification appears to be silent on any correlation between the in vitro testing and in vivo success. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

5. The quantity of experimentation necessary

Because of the known unpredictability of the art (see section 3) and in the absence of experimental evidence commensurate with the claims (see section 4), the skilled in the art will not accept that a combination of Imatinib and Flavopiridol or any CDK inhibitor will treat Imatinib resistant leukemia in humans in a synergistic way, as inferred by the claims and contemplated by the specification

6. Conclusion

Accordingly, the inventions of claims 17-22 do not comply with the f enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention, a person of ordinary skill in the art would have to engage in undue experimentation with no reasonable expectation of success.

Withdrawn Rejections and/or Objections

Claims rejected under 35 USC 103(a)

Applicant's arguments presented in the Declaration under 37 C.F.R. 1.132 have been fully considered and are persuasive. The prior art of Yu et. al. (Blood, Vol. 98(11), 2001:146a, abstract 615,) is by the same authors and was published lees than one year before filing of the instant application, as such does not qualify as prior art.

Rejection under 35 USC 103(a) is withdrawn.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
July 12, 2009

/Brandon J Fetterolf/

Primary Examiner, Art Unit 1642